REMARKS

Claims 1-42, 44-53, 55-66 and 70-76 are under consideration in the above-referenced patent application and have been rejected under 35 U.S.C. § 103, § 112 or both. Applicants respectfully request reconsideration and withdrawal of these rejections in view of the above amendments and the following discussion.

Claims 1 and 21 have been amended as indicated above. Claims 1 and 21, as amended, now state that the transduction or administration of drug may be performed *in vivo* or after the cells have been removed from the mammal from which they originated. Support for the amendment to Claim 1 is found throughout the specification, for example, at page 3, lines 15-17 and 21-25; page 4, lines 13-22 and 32-33; page 8, lines 12-15; page 20, lines 7-27; page 25, lines 24-25; and page 51, lines 25-32 and 34-35. The amendment to Claim 21 is supported throughout the application, for example, at page 8, lines 18-21; page 31, lines 2-10; page 34, lines 16-25 and 34-35; page 35, lines 4-7; page 42, lines 4-7, 12-21 and 31-33; page 45, lines 27-30; page 47, lines 1-2; page 49, lines 18-24; page 51, lines 2-4 and 17-18; and page 55, lines 16-18.

Claim 57 has been amended to correct a minor stylistic error. More specifically, "A method..." has been changed to "The method..." in the preamble of this dependent claim.

In view of the above comments, these amendments do not constitute the addition of new matter to the application.

Rejections under 35 U.S.C. § 103

Rejections over Capon et al. in view of Blau et al.

Claims 1-42, 44-53, 55-66 and 70-76 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,741,899 (Capon et al.) in view of Blau et al. (1997).

Capon et al. teaches various categories of chimeric proteins that comprise, *inter alia*, a signaling domain and a drug-responsive domain. Capon et al. further describes an experiment to test cell proliferation *in vitro* wherein cells expressing a chimeric protein are contacted with plates coated with a saturating concentration of an inducer drug, such as FK1012 (see, for example, Capon et al. at column 42, line 48 to column 43, line 12).

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In previous communications with the Patent Office, applicants asserted that Capon et al. does not provide an enabling disclosure because the Capon et al. assay would not be expected to work due to the use of too high a concentration of the inducing drug. In the Office Action of October 6, 2005, the examiner acknowledges that in view of applicant's third declaration, she is persuaded that Capon et al. does not demonstrate that "such a concentration or any other concentration is effective in inducing the proliferation of a primary cell type." Nonetheless, the examiner now asserts that the optimization of drug concentrations for dimerization of chimeric proteins is routine, relying on Blau et al. to demonstrate the relative effectiveness of using different concentrations of FK1012 to induce cells expressing a chimeric receptor.

Applicants disagree with the examiner's proposition that one attempting to perform the assay of Capon et al. would have known why the assay failed to work. It is pertinent that Capon et al. did not provide any examples other than prophetic examples to demonstrate the functionality of the described chimeric proteins. If one followed the teachings of Capon et al. and experienced failure of the test assay taught therein, this person would not know the source of the problem. There could be several reasons why the assay did not work. One possibility is the dimerizing agent itself. If the dimerizing drug does not bring the chimeric proteins sufficiently close to one another, or alternatively, brings them too close to one another, signal transduction would not occur. Additionally, fusing a signaling domain to a heterologous inducing domain might, upon dimerization, orient the signaling domain in a way that prevents it from assuming the conformation necessary to transmit a signal. If such were the case, the problem could not be fixed by adjusting the concentration of inducing drug. Since Capon et al. did not demonstrate the actual functionality of any of the described constructs, it would be reasonable for one skilled in the art, faced with a failed assay, to question whether the constructs were capable of functioning at all. In view of these considerations, it is unreasonable to assume that one skilled in the art would automatically expect the assay of Capon et al. to work if they simply lowered the concentration of inducer.

Moreover, Capon et al. was specific about what concentration should be used, that is, a "saturating" concentration, and one skilled in the art would expect this teaching to be reliable.

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Capon et al. did not teach or remotely suggest that one should utilize any other concentration, thus this reference provides no motivation for trying other concentrations. Given that Capon et al. teaches a particular concentration and further given that other reasons for the failed assay are possible, one skilled in the art would not automatically focus on changing the inducer concentration. To the contrary, they would expect a variety of experimental approaches to be necessary in order to discover why the assay failed. They would feel obliged to question every aspect of the assay, including the capabilities of the constructs themselves.

The above comments illustrate that the invention of claims 1-42, 59-66 and 70-76 are not obvious over the combination of Capon et al. and Blau et al. Accordingly, the examiner is respectfully requested to remove this ground for the rejection of these claims.

Rejections over Capon et al. in view of Crabtree et al. and Blau et al.

Claims 44-53 and 55-58 have been rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,741,899 (Capon et al.) in view of U.S. Patent No. 5,994,313 (Crabtree et al.) and Blau et al. (1997). Claims 44-53 and 55 pertain to genetically engineered cells encoding a fusion protein having at least one altered amino acid, while claims 56-58 pertain to methods for treating disease comprising administering to a mammal a cell of claim 46.

The examiner notes that Capon et al. differs from the claimed invention in that it does not teach that the inducer-responsive clustering domain of the chimeric protein comprises at least one amino acid change compared to the most prevalent naturally-occurring amino acid sequence. Capon et al. refers to the inducer-responsive clustering domain as the "ECD" or the "ICD" (column 4, lines 7-18). The examiner notes that Capon et al. (column 5, lines 12-15) suggest that modifications can be made to the "ICD" to create improved receptor-ligand binding. However, the "modifications" of Capon et al. are undefined, thus this teaching of Capon et al. is not the same as the invention claimed herein. Capon et al. does not teach or remotely suggest that one should introduce at least one amino acid change compared to the most prevalent naturally-occurring amino acid sequence of the drug-binding domain, as is recited in claim 44.

The examiner asserts that Crabtree et al. supplements Capon et al. by teaching chimeric proteins comprising an inducer-responsive clustering domain and a signaling domain wherein the

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inducer-responsive domain of FKBP12 contains specific amino acid changes as compared with the wild-type sequences. However, as discussed further below, one skilled in the art would have no motivation to combine the teachings of Crabtree et al. with the teachings of Capon et al. Accordingly, the invention described herein is not obvious over Capon et al. taken in view of Crabtree et al.

Blau et al. (1997) is cited as part of this combination for teaching that responsiveness to FK1012 can be affected by the concentration of drug. However, as noted above, Capon et al. teaches a particular concentration that should be used (a "saturating" concentration) and does not suggest that any other concentration should be substituted. One skilled in the art would expect this teaching to be reliable. If one following the teachings of Capon et al. found that the test assay did not work, they would have to engage in undue experimentation to discover the reason why. This skilled artisan would not proceed any further until they had devised a workable assay, thus they could not reach the point of considering modifications to the ICD or ECD until after having engaged in undue experimentation. Accordingly, even if the teachings of Capon et al. were combined with Crabtree et al. and Blau et al., there would be no reasonable expectation of success.

In view of the above, it is believed that claims 44-53 and 55-58 are not obvious over the combination of Capon et al., Crabtree et al. and Blau et al. Accordingly, the examiner is respectfully requested to withdraw the rejection of these claims over this group of references.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 12-20 and 32-40 have been rejected under 35 U.S.C. § 112, second paragraph.

Claims 12 and 32 are said to be unclear because there is no antecedent basis for "wherein the cells are removed from the mammal." Claims 13-20 and 33-40 are included in this rejection because they depend directly or indirectly from claims 12 or 32. This concern has been addressed by amending claims 1 and 21, from which claims 12 and 32 respectively depend, in order to provide the required antecedent basis. Accordingly, it is respectfully requested that this ground for the rejection of claims 12-20 and 32-40 be withdrawn.

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Claim Objections

Claim 57 has been objected to because it recites "A method of Claim 56." Claim 57 has been amended as shown above to recite instead "The method of Claim 56." The examiner therefore is asked to remove this objection to Claim 57.

Oath/Declaration

The examiner has asserted that the declaration on file in this application is defective because it fails to state that the application claims the benefit of priority form U.S. provisional applications 60/070/754, filed January 8, 1998; 60/070,893, filed January 9, 1998; and 60/102,888, filed October 2, 1998. A corrected declaration is attached hereto.

CONCLUSION

In view of the foregoing remarks and amendments, Claims 1-42, 44-53, 55-66 and 70-76 are believed to be in condition for allowance. The examiner therefore is respectfully requested to remove all remaining grounds for rejection and to allow these claims. If any issues remain that can be expeditiously addressed in a telephone interview, the examiner is urged to contact the undersigned at her direct dial number given below.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: March 1, 2006 _____ DXS:jlb

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